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γ-Promotion of thermal stability and radiolysis mechanism of atenolol β-blocker

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Abstract

Atenolol (At) β-blocker antihypertensive active ingredient has been investigated for its X-ray diffraction analysis, thermogravimetric analysis (TGA), differential thermal analysis (DTA), IR-absorption spectra and electronic absorption spectra (UV–VIS) before and after exposure to γ-radiation doses. The results obtained indicated high resistance of the material against γ-irradiations. The specific γ-absorbed doses (40 and 60 kGy) induced higher resistance to γ-irradiation. Finally the mechanism of γ-radiolysis is putforward and achieved. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: γ-Radiolysis; X-ray diffraction; Compton effect

1. Introduction

Atenolol (At) is 4-(2-hydroxy-3-isopropylamino-propoxy)phenyl acetamide (Scheme 1), is one of a number of drugs collectively known as β-blockers.

Its pharmaceutical action is the management of hypertension, angina pectoris, where it acts preferentially upon the β-adrenergic receptor in the heart [1]. A review article of At and its dimerization was given [2].

Radiation effects in solids are subjects of great importance to investigate one or more features of the decomposition process [3–6].

In irradiation with ^{60}Co γ-rays, the Compton effect has the largest-cross-section [7] except for materials of very high atomic number and diminishes [8] to zero around atomic weights of 125. ESR study of radio sterilization of antibiotics was carried out on γ-ray irradiated cefazidime and ampicillin [9,10]. The effect of γ-radiation on the degradation of salbutamol was evaluated [10]. The thermal stability of γ-irradiation of tolbutamide was studied [11]. Process control and dosimeter in multipurpose irradiation facility were carried out [12]. The ESR spectroscopy was applied to the study of pharmaceuticals radio sterilization of cefoperzone [13]. In the present article X-ray, IR spectra γ-irradiations, thermogravimetric analysis (TGA), differential thermal analysis (DTA) has been undertaken on At β-blockers.

The major goal of the present manuscript is to enhance and promote thermal stability, and hence, to lengthen the expiry time by γ-irradiations. This in addition throws a light on the γ-pyrolysis.

2. Experimental

Atenolol (At) is a pure substance and satisfies US pharmacopoeia requirements. All chemicals used are

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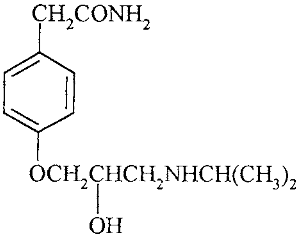
of analytical pure grade (purity 99.5%). The X-ray diffraction patterns (2θ (°/min)) were recorded with a Philips X-ray diffractometer (UK) using Cu Kα radiation. TGA and DTA measurements were carried out using XD-30 Thermal Analyzer in air up to 500 °C and heating rate 10 °C. The IR-absorption spectra were recorded using KBr pellets and a Shimadzu (Japan) Spectrophotometer in the range (4000–200 cm^{-1}). Perkin-Elmer UV–VIS. Spectrophotometer was used for electronic absorption in the range (200–400 nm) and ethanolic solution. A group of samples of At (five samples) were irradiated with different γ-doses ranging from 5 up to 60 kGy using Cs-137 source (Table 1). The dose rate was 0.4 cGy/s at a distance of 30 cm from the source in air.



Scheme 1.

Table 1
γ-Doses absorbed to At β-blocker

No.	Dose (kGy)
a	0.000
b	5
c	20
d	40
e	5
f	60

3. Results and discussion

Fig. 1 represents results of X-ray diffraction studies of material under investigation before and after γ-doses. We can suggest the following senior author mechanism confirming that the conditions are kept identical for all samples.

At + first dose 5 kGy	The degree of crystallinity suffers weakening due to partial dissociation (Fig. 1b).
At + second dose 20 kGy	Further dissociation, γ-enhanced melting resulted in a decreased degree of crystallinity as reflected from the weakening of X-ray diffraction peak intensities (Fig. 1c).
At + third dose 40 kGy	γ-Enhanced back recombination of the formed free radicals or the dissociated species gave high degree of crystallinity and this reflected from the strengthening of X-ray diffraction peak intensities due to the high counts value (Fig. 1d).

After γ-absorbed doses up to 60 kGy the X-ray diffraction patterns still belong to the pure structure of At [14]. After the first γ-absorbed dose (5 kGy) the relative intensity (counts) of the diffraction peaks suffer a decreased peak intensity due to the partial dissociation of the material as induced by γ-absorbed dose. After the second, absorbed dose (20 kGy) the relative intensity suffers further decreased intensity. After the third γ-absorbed dose (40 kGy), the X-ray peak intensity increases again to a maximum value preserving the material identity.

This increased X-ray peak is due to intensity of the increased degree of crystallinity as caused by γ-induced free radical recombination, and hence, polymerization besides, γ-induced thermal heating of At β-blocker (see Fig. 2).

3.1. Thermal stability (TGA and DTA)

Table 2 and Fig. 3 show a collection of thermal analysis TGA and DTA results of At as a function of γ-absorbed dose before (a) and after (b)–(f) γ-absorbed dose. These include temperature range, weight loss, assignment and ΔH. It can easily be seen that the TGA and DTA curves of At belong to the pure structure of At in agreement with that previously given by Caplar et al. [15]. It can easily be seen that all behavior for the various γ-absorbed doses above 200 °C are not identical. Thus, it was emphasized that above 200 °C, the DTA spectra are not identical for all samples due to

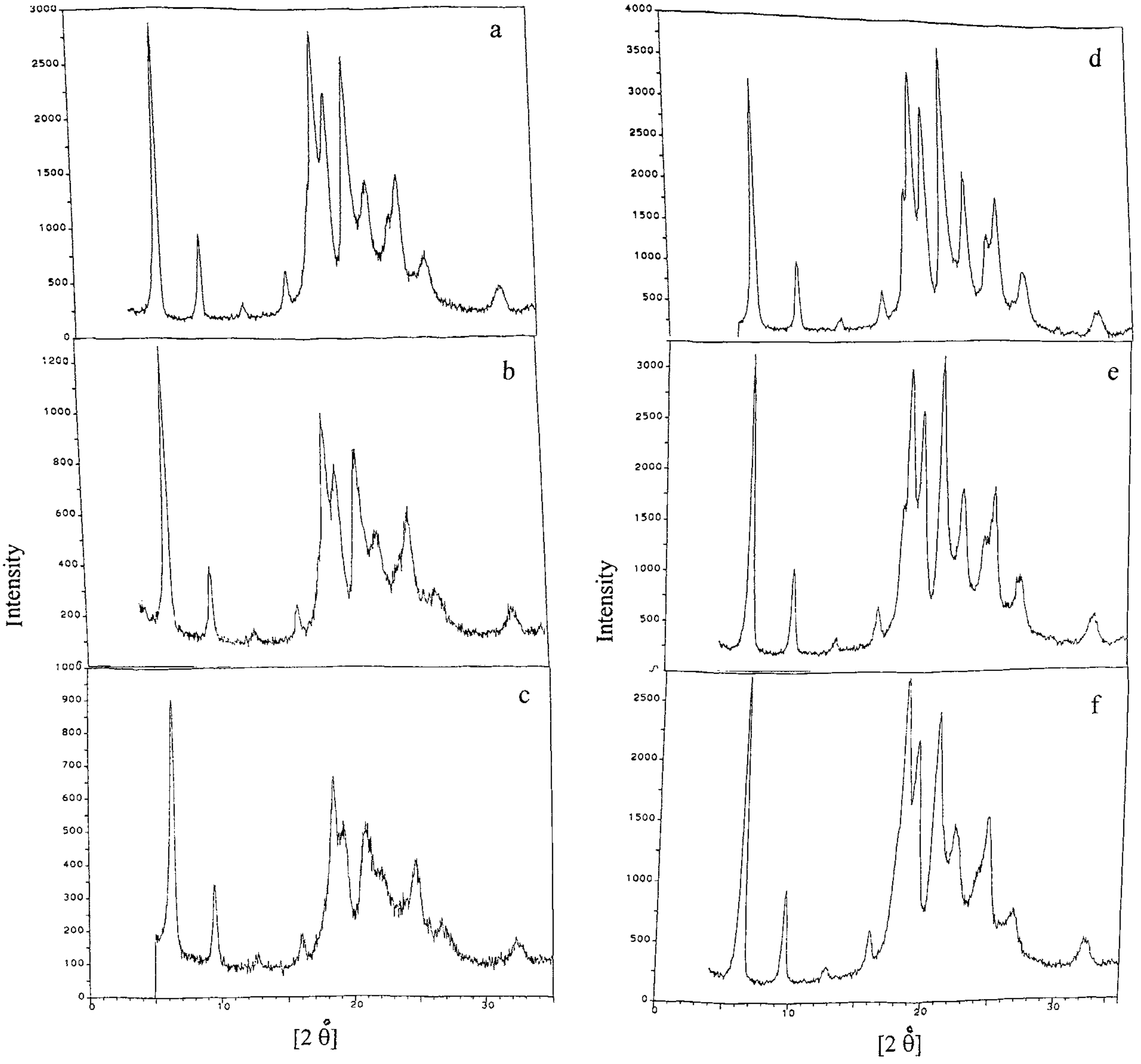


Fig. 1. X-ray diffraction patterns of At, β-blocker: (a) before γ-irradiation; (b) after γ-absorbed (5 kGy) dose; (c) after γ-absorbed (20 kGy) dose; (d) after γ-absorbed (40 kGy) dose; (e) after γ-absorbed (50 kGy); (f) after γ-absorbed (60 kGy) dose.

γ-radiation damage extent which depends on the absorbed dose.

3.2. Results of IR studies

Fig. 4 and Table 3 display the IR spectra of At before (a) and after (b)–(f) γ-absorbed doses from 5 up to 60 kGy (b)–(f). The IR peaks of At before and after γ-irradiation were assigned as follows: 3340, 3160 cm^{-1} (–CO–NH), 2940 cm^{-1} (=C–H), 1652 cm^{-1} (–C=C), amide, 1500 cm^{-1} (–N–C=O, amide), 1400 cm^{-1} (H_2N–CO–), 1385 cm^{-1} (I–Pr), 1390, 1235, (aryl ether) 1170 cm^{-1} (I–Pr), 1105, 1080, 1030, 910, 880, 810, 740, 700, 660 cm^{-1}

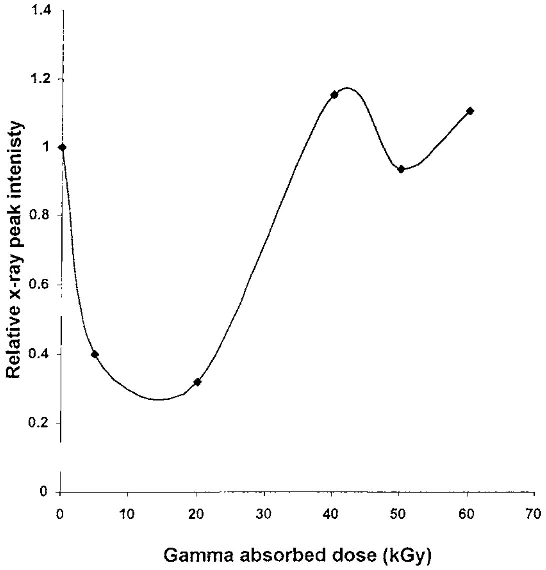


Fig. 2. The variation of relative peak intensity of X-ray vs. γ-absorbed dose for At β-blocker at 2θ 6.4°.

dimeric compound(s). From these results as in Fig. 4, the IR-absorption spectra suffer: (a) decreased intensity of peak after dose 5 kGy; (b) increased intensity of peak after dose 40 kGy. These results are supported from X-ray data.

3.3. Electronic absorption spectra

The effect of γ-irradiation doses on the electronic absorption spectra of At was studied by using 20 μg ml^{-1} in anhydrous ethanol in the range 200–400 nm. Thus, Fig. 5 represents the relation between electronic absorption (UV) and the absorbed γ-doses. For At before and after γ-irradiation the spectra in all cases (273.5 nm) indicate that the material still preserves its identity after γ-absorbed doses. The variation of optical density of the spectra with γ-absorbed doses displays the same trend exactly depicted from our preceding X-ray and IR spectral data.

Table 2
Thermal behavior (TGA and DTA) and their assignment for At before and after γ-irradiation

Material	TGA data		DTA data		
	Temperature range (°C)	Weight loss (%)	Assignment	Temperature range (°C)	ΔH (kJ/g)
Before γ-irradiation	157.8		Endothermic peak due to melting	133.6–180.2	−118.6
	215–490	76.2	Exothermic peak due to stepwise oxidative decomposition	290–321	−141.4
				315–343	16
				426–444	−19
After γ-absorbed (5 kGy)	157.5		Endothermic peak due to melting	131.7–175.7	−105.5
	220–498.1	71.8	Exothermic peak due to stepwise oxidative decomposition	410–436	−13.7
			Endothermic peak due to dissociation of oxidation products	441–447	−1.64
After γ-absorbed (20 kGy)	156.7		Endothermic peak due to melting	139.6–175.8	−153.6
	220–498	75	Exothermic peak due to stepwise oxidative decomposition	307–341	43.8
			Endothermic peak due to dissociation of oxidative products	3.67	64.8
After γ-absorbed (40 kGy)	158.4	74.5	Endothermic peak due to melting	137.4–176.6	−151.9
	228–498		Exothermic peak due to stepwise oxidative decomposition	300–385.5	334.8
			Endothermic peak due to dissociation of oxidative products	458–488	−51.84
After γ-absorbed (50 kGy)	158.4		Endothermic peak due to melting	139–180.6	−162.4
	225–499	75.4	Exothermic peak due to stepwise oxidative decomposition	326–380	18.9
			Endothermic peak due to dissociation of oxidative products	435.4–470	−152.4
After γ-absorbed (60 kGy)	157.9		Endothermic peak due to melting	138–179	−150
	225–499	75.4	Exothermic peak due to stepwise oxidative decomposition	325–385	20
			Endothermic peak due to dissociation of oxidative products	430–474	−151

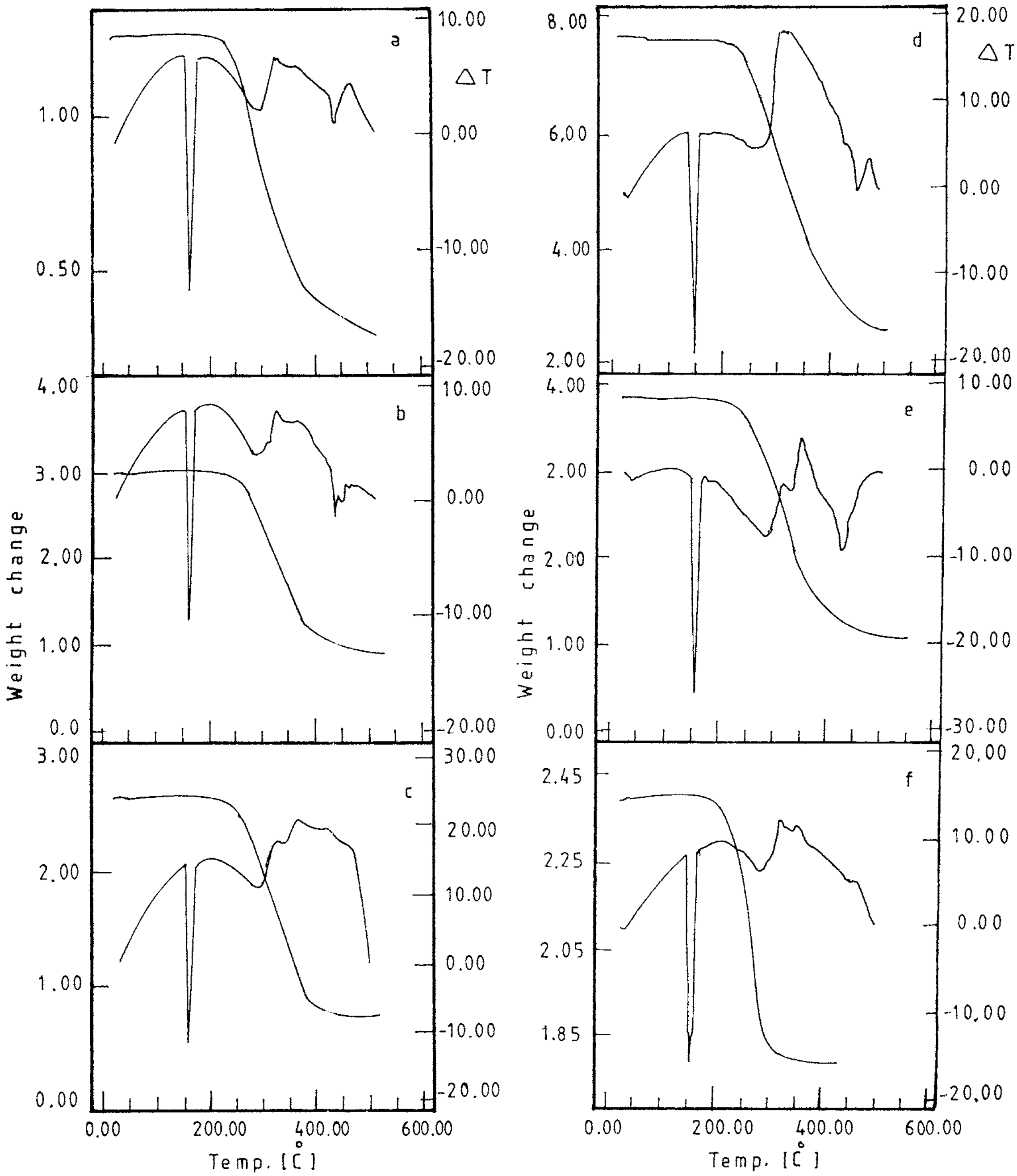


Fig. 3. The variation of TGA and DTA of At β-blocker as a function of γ-absorbed doses: (a) before γ-irradiation; (b) after γ-absorbed (5 kGy) dose; (c) after γ-absorbed (20 kGy) dose; (d) after γ-absorbed (40 kGy) dose; (e) after γ-absorbed (50 kGy) dose; (f) after γ-absorbed (60 kGy) dose.

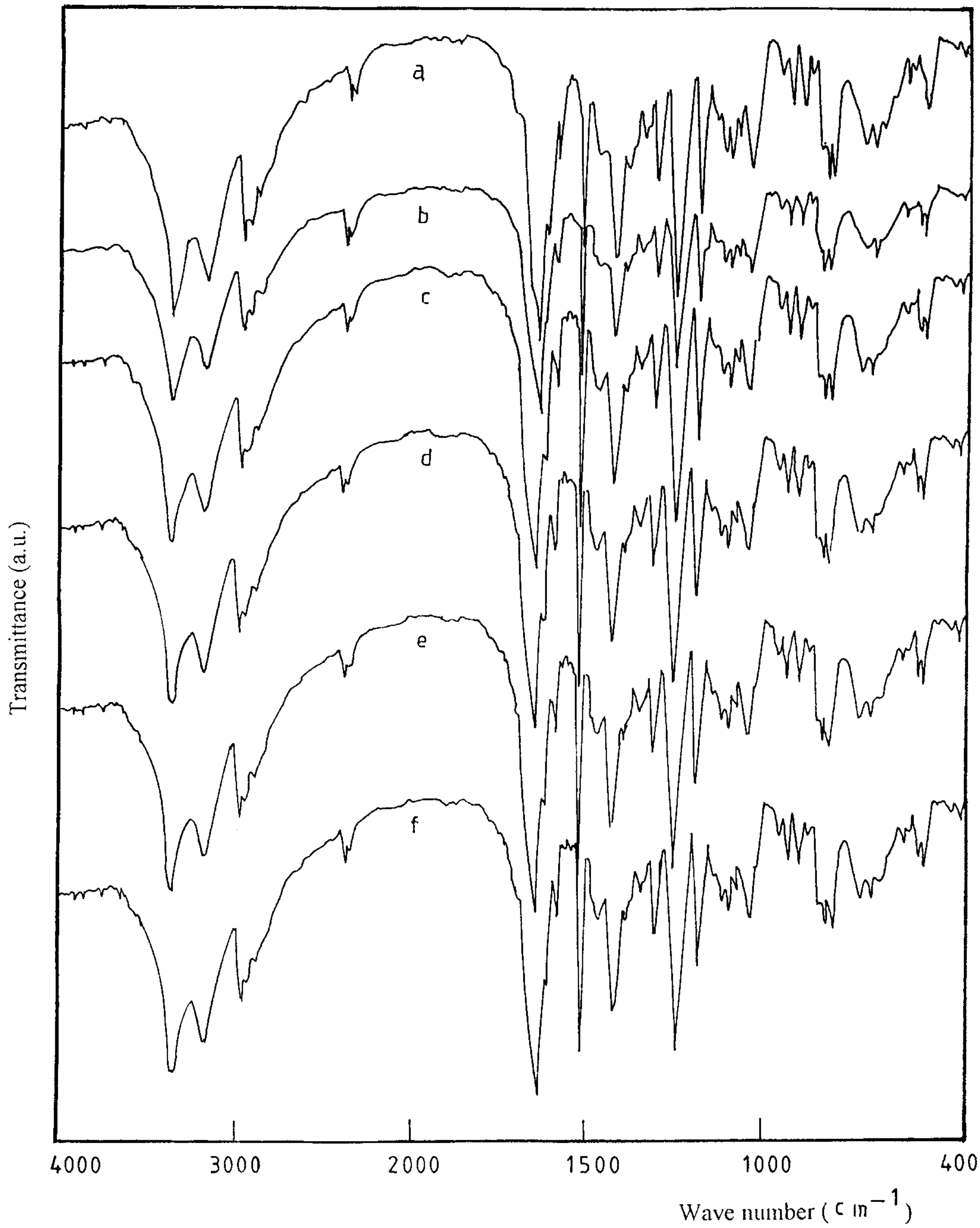


Fig. 4. IR-absorption spectra of At β-blocker at various γ-absorbed doses: (a) before γ-irradiation; (b) after γ-absorbed (5 kGy) dose; (c) after γ-absorbed (20 kGy) dose; (d) after γ-absorbed (40 kGy) dose; (e) after γ-absorbed (50 kGy) dose; (f) after γ-absorbed (60 kGy) dose.

Table 3
The characteristic IR-absorption spectra and their band assignment of At β-blocker at 5 up to 60 kGy γ-absorbed doses

Dose						Assignment
0.0 kGy	5 kGy	20 kGy	40 kGy	50 kGy	60 kGy	
Absorption band (cm^{-1})						
3340, 3160	3340, 3160	3340, 3160	3340, 3160	3340, 3160	3340, 3160	–CO–NH
2940	2940	2940	2940	2940	2940	=C–H
1652	1652	1652	1652	1652	1652	–C=C, amide 1
1500	1500	1500	1500	1500	1500	–N–C=O, amide 2
1400	1400	1400	1400	1400	1400	H_2N–CO–
1385	1385	1385	1385	1385	1385	I–Pr
1390, 1235	1390, 1235	1390, 1235	1390, 1235	1390, 1235	1390, 1235	Aryl ether
1170	1170	1170	1170	1170	1170	I–Pr
1105, 1080	1105, 1080	1105, 1080	1105, 1080	1105, 1080	1105, 1080	Dimeric and polymeric compound [15]
1030, 910	1030, 910	1030, 910	1030, 910	1030, 910	1030, 910	
880, 810, 790	880, 810, 790	880, 810, 790	880, 810, 790	880, 810, 790	880, 810, 790	
700, 660	700, 660	700, 660	700, 660	700, 660	700, 660	

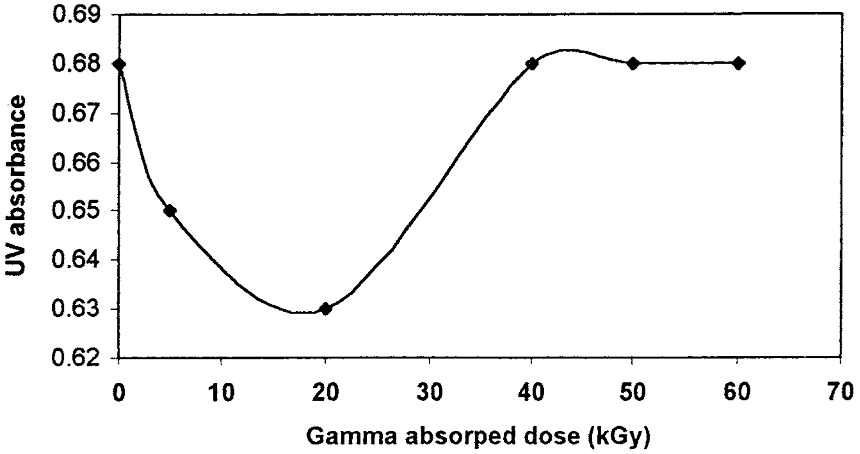


Fig. 5. Relation between electron absorbance (UV) and γ-absorbed dose of At β-blocker.

4. Conclusion

Atenolol (At) β-blockers display high resistance to nuclear γ-absorbed dose from 20 up to 50 kGy throughout a γ-induced polymerization mechanism. Results and discussion given by X-ray, thermal analysis, IR spectra and electronic absorption (UV–VIS) lead to good analysis support of one another. Alternatively γ-absorbed dose 40 kGy could be used safely for sterilization and extension of expiry date of At β-blocker for special application.

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